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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/853,292	05/09/97	TOVEY M	23164-1003

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EXAMINER	
ANDRES, J	
ART UNIT	**PAPER NUMBER**
1646	24

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/853,292	TOVEY, MICHAEL GERARD	
	Examiner	Art Unit	
	Janet L Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13,19-23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13,19-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on January 16, 2001 under 37 CFR 1.114 based on parent Application No. 08/853292 is acceptable. An action on the RCE follows.

Applicant's amendment of November 27, 2000 has been entered in full. Claims 1-5, 7-13, 19-23, and 25 are pending in this application.

2. Although claim 1 includes the limitation "oromucosal administration ...not administered through the mouth", this claim is deemed to be properly limiting because of Applicant's definition of "oromucosal" on page 11 of the specification, which clearly indicates that "oromucosal" includes intranasal administration.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-5, 7-13, 19-23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Cummins (U.S. patent 5019382, 1991) or Cummins (U.S. patent 5830456, 1998, filed September, 1994) in view of either Samo et al.(J. Infect.Dis., 1984, vol. 150, pp. 181-188) or Iida et al.(Vaccine, 1989, vol 7, pp. 229-233).

In each patent, Cummins teaches the use of interferons contacting the oral mucosa to treat neoplastic disease, viral disease, and bacterial infection (columns 4 and 5 of '382, or the whole document, particularly columns 4, 5, 13, and 14, of '456). However, Cummins teaches a maximum dose of 5 IU/lb/day, or 11 IU/kg/day, whereas the instant claims encompass a range of 21.4 IU/kg/day to about $2.9x10^4$ IU/kg/day. Samo et al. teaches a range of $0.7\text{-}2.4x10^6$U (not IU, as was erroneously noted in previous office actions). Accepting Cummins' definition of a unit

(U) as being 0.1 international units (IU) (column 3, line 56 of each patent), this range is equivalent to 0.7-2.4x10^5 IU/kg/day. Iida et al. teaches a range of 10-10^3 U/mouse (also erroneously referred to as 10-10^3 IU in previous actions) administered on one day, intranasally (p. 230). Assuming 30g/mouse, this is a range of .3-300 U/g, or 30-3000 IU/kg, again relying on Cummins' definition of a unit. Thus the range taught by Iida et al. overlaps the instant range, and the range taught by Samo et al. is higher. Neither Samo et al. or Iida et al. teaches treatment; these references are drawn to prophylaxis. However,

In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom. In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968).

In each patent, Cummins discloses a broad range, more than two orders of magnitude, of oromucosal doses effective for treatment of viral infections. Samo et al. and Iida et al. teach that much higher oromucosal doses are used therapeutically in the art. One of ordinary skill would therefore reasonably expect that doses higher than those taught by Cummins would be effective in treatment of viral infection. Thus, becuase Samo et al. and Iida et al. teach that it was known in the art to administer much higher doses, it would have been *prima facie* obvious for one of ordinary skill to administer doses higher than those taught by Cummins with an expectation of achieving a result at least as good as that achieved by Cummins.

Applicant has traversed this rejection, as made in previous office actions, beginning on p.5 of the communication of paper 21, filed November 17, 2000. Previous actions presented only the '382 patent and Applicant's traversal thus considers only this reference. However, the arguments presented are relevant to the '456 patent as well. This patent incorporates much of the specification of the '382 patent; it differs in that it more specifically addresses anti-viral uses of

oromucosally administered interferon. Thus the teachings of the '456 patent are considered in the Examiner's response to Applicant's arguments.

Applicant states on p. 5 that the examiner refused to consider Applicant's post-filing date evidence that Cummins teaches away from higher doses. The examiner did not refuse to consider the reference; as stated on page 5 of the office action of July 18, 2000, in paper no. 20, Applicant's argument was not found to be persuasive, because post-filing date evidence is irrelevant to what one of ordinary skill would have known at the time of filing.

Applicant states that Cummins teaches a maximum of about 5 IU/kg/day. The examiner observes, however, that Cummins teaches a maximum of 5 IU/**lb**/day (see abstract and column 4, lines 15 and 26). This is equivalent to 11 IU/kg/day. The range described by Cummins spans more than 2.5 orders of magnitude (column 4, line 26) and the lowest dose in the instant claims is less than twice the highest dose taught by Cummins, and is further well within an order of magnitude of the highest dose taught by Cummins. Thus the lowest dose taught by Applicant would not seem to be significantly different from that taught by Cummins, particularly in view of the secondary references of Samo et al. and Iida et al., which teach that higher doses are known in the art. Applicant argues that the teachings of Samo et al. and Iida et al. would not suggest to one of ordinary skill the use of larger amounts than those suggested by Cummins, since these teachings are limited to prophylaxis rather than treatment. However, the Cummins patents serve to teach treatment of pre-existing conditions; the teachings of Samo et al. and Iida et al. are referenced only as evidence that therapeutic use of higher doses of interferon, administered by mucosal contact, was known in the art at the time the invention was made. Thus since Cummins teaches a range spanning 2.5 orders of magnitude to treat disease, and Samo et al. and Iida et al.

teach that doses equal to and higher than Applicant's highest doses were known in the art to be used therapeutically, it would have been obvious to one of ordinary skill to use doses higher than those taught by Cummins.

Applicant further argues, beginning on p. 6, that Hayden et al. and Scott teach away from use of interferon in the treatment of rhinovirus, and that there is thus no motivation to combine the teachings of Cummins with the secondary references teaching prophylaxis. However, Cummins does teach treatment of rhinovirus (column 5, line 13), at doses that do not appear to differ significantly from the lower end of Applicant's claimed range, as stated above. Further, the instant claims are not limited to rhinovirus, but encompass any pathologic condition. The art as a whole teaches that interferons are useful for the treatment of pathological conditions, for example hepatitis, for which interferons are standard treatment (see Wong et al., Ann. Intern. Med., 1995, vol. 122, pages 664-675, and Malaguarnera et al., Curr. Ther. Res., 1996, vol. 57, pages 646-662). Thus the art does not generally teach away from treatment of pre-existing conditions with interferons and therefore does not teach away from the combination of a reference teaching such treatment with references teaching higher doses as prophylactic.

Applicant further argues that Cummins, in U.S. patent 4820515, teaches away from higher doses. However, what Cummins appears to teach is that higher doses are not better than lower doses, not that they are not effective. Further, this patent provides explicit support for the use of higher doses, as 18 IU/lb is nearly 40 IU/kg. In the later review cited by Applicant (J. Int. Cyt. Res., 1999, vol. 19, pages 853-857), Cummins again does not teach that increasing the dose was harmful, only that it did not improve the effect. Further, in the '382 and '456 patents, Cummins defines neither a high dose nor a low dose; these are relative terms that are undefined

and not used as limitations in the specification or in the claims. It is not necessary for a higher dose to have been Cummins' preferred embodiment for the '382 and '456 patents to provide a teaching of obviousness.

Applicant further cites the teachings of Moore et al. (Vet. Immunol. Immunopathol. 1996, vol. 49, pages 347-358). Moore et al., however, teaches units (U), not IU. As discussed above, in the '382 and '456 patents Cummins teaches that a unit is 0.1 IU. Cummins is a coauthor of the Moore publication; absent teachings to the contrary, the Examiner assumes again that 1 U, as taught by Moore et al., is 0.1 IU. 450 units/horse would thus be 0.1 IU/kg (assuming a 1000 lb or 450 kg horse) and the highest dose is less than half the lowest dose taught by Cummins (0.1 IU/lb/day, thus 0.22 IU/kg/day, see abstract) and more than two orders of magnitude lower than what is claimed in the instant application. Thus the small variation in effect observed between 150 and 450 units taught by Moore et al. is not relevant to the ranges taught by either Cummins patents or the instant application, which are two- to one hundred-fold higher; considered as a trend and extrapolated, this variation would suggest that even the doses taught by the Cummins patents would be ineffective. Clearly, they are not: Cummins, in the '382 patent, (column 8, line 23) discloses effective treatment of parvovirus with 4 IU/lb or 9 IU/kg, three times daily, thus 27 IU/kg/day, more than two orders of magnitude higher than the highest dose taught by Moore et al.

Applicant refers on page 9 to comparative results indicating that no biologically active interferon enters the bloodstream after oromucosal dosage, and concludes that the mechanism of action of oromucosal administration is different from that of parenteral administration. Applicant argues, therefore, that parenteral doses are not relevant to the instantly claimed form of

administration. The Examiner agrees. All references cited in this action are specifically drawn to oromucosal administration.

Applicant further argues beginning on page 10 that the administration of interferon by an oromucosal route does not involve a direct action of exogenously administered interferon, and that one of ordinary skill would not have considered administering interferon in this way. Applicant states that migration of immunocompetent cells is stimulated by oromucosal administration and is the mechanism of action of the claimed method. However, the mechanism of action is not the subject of the claims; what is claimed is a method of oromucosal administration. While the claims limit to a mechanism, there are no method steps to achieve this specific mechanism. Further, Cummins, in each patent, anticipates a systemic effect. The '382 patent teaches that "a patient experiencing viral myocarditis has responded favorably to the present treatment" and that "warts often dissipate within six to eight weeks after initiating treatment in accordance with this invention" (column 5, lines 20-24). The '456 explicitly teaches treatment of diseases of viral origin requiring a systemic effect, including canine parvovirus, canine herpesvirus, feline leukemia, feline infectious peritonitis, rhinovirus, papovavirus, and herpes simplex I using oromucosal administration of interferon (column 5, lines 1-29). Thus, although neither patent presents a mechanism of action, Cummins clearly teaches a systemic result from oromucosal administration in both patents.

Applicant argues on p. 11 that the only reference to suggest oromucosal administration is Cummins, that Cummins elsewhere teaches away from higher doses, and that one of ordinary skill would not expect interferon to enter the bloodstream. The Examiner interprets this statement to mean, again, that it would not be obvious to combine other references with the '382

patent to use higher oromucosal doses. However, as stated above, Cummins teaches only that higher doses are not better. Further, Cummins, in the '456 patent, clearly does expect oral interferon to have a systemic effect. Claims 5 and 6 of the '456 patent are drawn to methods wherein the interferon is administered "in contact with the patient's oral and pharyngeal mucosa for delivery of the interferon to the patient's lymphatic system to stimulate an anti-viral response" (column 14, lines 33-63). Thus Cummins in each patent teaches oromucosal administration to treat viral infections and, implicitly in the '382 patent, since treatment of myocarditis and papovavirus are disclosed, and explicitly in the '456 patent, contemplates a systemic response. Thus one of ordinary skill would expect a systemic effect, regardless of the mechanism of the effect. Applicant concludes that there is no motivation to "substantially increase" the maximum dose taught by Cummins. However, as noted on pages 3 and 4 of this action, Applicant's lowest dose is less than two-fold greater than the highest dose taught by Cummins in each patent. Since Cummins' range spans more than two orders of magnitude, and Samo et al. and Iida et al. teach that much higher oromucosal doses are known in the art, a doubling of the dose would not seem to be a substantial increase. Absent any explicit teaching that such an increase would be harmful, and given that Samo et al. and Iida et al. teach that much higher doses, administered similarly, were known in the art, one of ordinary skill would expect higher doses than those taught by Cummins in the '382 and '456 patents to be useful in the systemic treatment of viral infections.

Thus, it would have been obvious to one of ordinary skill in the art to combine the teachings of Cummins, in either the '382 or '456 patent, with those of Iida et al. or Samo et al. to administer higher oromucosal doses than those taught by Cummins to treat viral disease. One of

ordinary skill would have been motivated to do so because Cummins teaches a broad range of doses, and Samo et al. and Iida et al. each teach that higher doses were known in the art to be administered by the same route (oromucosally) for therapeutic purposes.

Applicant discusses, beginning on page 11, the teachings of Hayden et al. (Antimicrob. Agents and Chemotherapy, 1988, vol. 32, pages 224-230) and of Eby (U.S. patent 5286748, 1994). Applicant states on p. 12 that the claims have been amended to require that the administration be in a manner that does not involve direct contact with virally infected cells. As stated above, the claims, while including a limitation on the mechanism of action, do not include a method step to ensure such a mechanism. Regardless, the teachings of Hayden et al. do not appear to be relevant as prior art, since Hayden et al. teaches only failure of a nasal spray as a treatment for rhinovirus. As discussed above, the instant claims are not limited to rhinovirus but encompass any pathologic condition. Since, as stated above, the art as a whole teaches that interferons are useful for treatment of pathological conditions, including viral infections, the Examiner is of the opinion that the teachings of Hayden are not pertinent to the issues and declines to make this reference of record. If Applicant feels differently, an information disclosure statement and form 1449 may be filed. Applicant further states that Eby teaches frequently repeated or continuous contact and additionally teaches that such continuous contact is necessary. Applicant states on p. 13 that Eby "believes that his invention is operable because of "absorption" of interferon." Regardless of Eby's perception of the mechanism of action, the examiner agrees that the teachings of Eby are not pertinent, since neither Cummins' nor Applicant's invention require such a mode of administration, whereas Eby clearly teaches that such administration is necessary. Thus, Eby is not the closest art to the claimed invention.

Applicant further cites the patent of Sato, on p. 13. The Examiner agrees that cancellation of the composition claims obviates a rejection based on the teachings of Sato.

Claim Rejections - 35 USC § 112.

5. Claims 1, 3-5, 7-13, 22, 23, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The negative limitation that the administration not involve direct action is a limitiaton on the mechanism with no corresponding method step to achieve that outcome.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 305-3014 or (703) 308-4242.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly

signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
February 23, 2001

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER